Overview

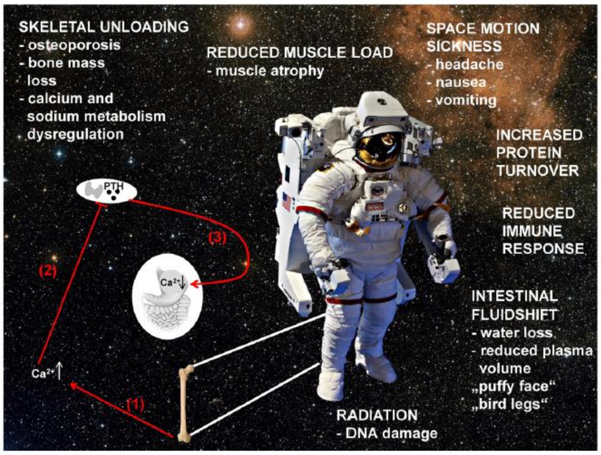
Bone density loss in microgravity (skeletal unloading) has been a well-documented crew health concern since the Skylab mission when it was observed that the flight crew having about 1-1.5% mineral loss per month. This was noted as being "significantly faster than normal osteoporotic individuals." As a result, several standards throughout Volume 1 and 2 of NASA-STD-3001 provide the various countermeasures that can aid in the prevention in the deterioration of the overall crew heath. Additionally, not only will these contribute to overall mission success, but they can provide benefits to other areas, including the crew mental well-being. Countermeasures like exercise, adequate nutrition and medications, have been recommended or required in an attempt to prevent the demineralization, especially with longer missions, like that of planetary and deep-space exploration.

Presently, as it is stated in the NASA-STD-3001 Volume 1, section 4.2.9 Permissible Outcome Limit for Microgravity-Induced Bone Mineral Loss Performance Standard (Baseline with Measured T-score), the standards noted address the range of acceptable loss. Appendix F.8 states the WHO definition of a normal BMD score, which used for determining crew BMD as stated in Volume 1 in 4.2.9, as noted below. The need for appropriate nutrition to prevent additional loss from various areas of concern, including that of the skeletal, muscular and immunological systems, which are easily impacted by a loss of micronutrients is supported by Appendix F.6. These values are related to the standards mentioned in 4.2.7 Permissible Outcome Limit for Nutrition Standard.

Standards

Volume 1

- 4.2.9.1 Crewmembers' pre-flight bone mass Dual Energy X-ray Absorptiometry (DEXA T) score **shall** not exceed -1.0 (-1.0 Standard Deviation (SD) below the mean Bone Mineral Density).
- 4.2.9.2 Countermeasures **shall** be aimed at maintaining bone mass in-flight consistent with outcome limits.
- 4.2.9.3 The post-flight (end of mission) bone mass DEXA T score **shall** not exceed -2.0 (-2.0 SD below the mean Bone Mineral Density).
- 4.2.9.4 Post-flight rehabilitation **shall** be aimed at returning bone mass to pre-flight baseline.



Grimm et al.

- F.6 Permissible Outcome Limit for Nutrition Standard - Key areas of clinical concern for long-duration space flight and exploration-class missions include loss of body mass, bone and muscle loss, increased radiation exposure, and general inadequate food intake.
- F.8 Permissible Outcome Limit for Microgravity Induced Bone Mineral Loss Performance Standard - Bone loss is a consistent finding of space flight and, for a 6-month mission, averages 1 percent loss per month at the lower spine and hip locations. Bone loss does show great variability among individual astronauts and between various bone locations. Countermeasures to prevent or mitigate bone loss include exercise, pharmacological agents, and nutrition. It is expected that partial gravity missions will have bone loss rates less or equal to those seen on ISS flights.

Additionally, the standards noted in Volume 2 section 7 support the bone loss prevention with the need of specific food quality and accommodations for exercise equipment.

- 7.1.1 Food Quality and Quantity[1]

  [V2 7006] Food Micronutrients - The diet for each crewmember **shall** include micronutrients in the quantities listed in table 13, Micronutrient Guidelines for Space Flight.

- 7.4 Physiological Countermeasures

  [V2 7038] Physiological Countermeasures Capability - The system **shall** provide countermeasures to meet crew bone, muscle, sensory-motor, and cardiovascular standards defined in NASA-STD-3001, Volume 1.

  [V2 7039] Volume Accommodations - During physiological countermeasure activities, volume **shall** be provided that is large enough to accommodate a person, expected body motions, and any necessary equipment.

1. Food and Nutrition Technical Brief

Background

Post-flight recovery of the bone loss and demineralization can occur over a period of time, but the long-term effects (increased risk of osteoporosis) of these changes on the crew are not completely understood, especially for the crew into their later years following long-term flights. As missions increase in duration, the prevention of this bone loss is necessary to avoid injuries or fractures to the crew, especially as more strenuous activities are performed and risks are increased with the exploration of other planetary bodies and longer durations of microgravity. As noted in HIDH 5.2.4.2 “it is critical for crewmembers to have frequent access (potentially multiple daily sessions) to exercise equipment that can provide high levels of loading, and diversity in load application, on the skeletal system. These exercise countermeasures should be targeted primarily toward protecting the lower body and hip regions.” It has been observed, that the areas of most concern are located in the lower areas of the body (i.e. hips and trochanter) due to the skeletal unloading.

As mentioned by Shackelford et al “Spaceflight can be considered as the ultimate model to determine the role of gravity on the human skeleton. There is a consensus among exercise scientists that both endurance (aerobic) and resistance exercises are needed as countermeasures to maintain overall crew health and performance during and after spaceflight. An exercise countermeasure has the advantage of benefiting multiple body systems (musculoskeletal, cardiovascular, immunological) and can be targeted to those body regions needing protection. Maintenance of muscle strength also reduces risk of injury during falls and impact. Increased muscle strength reduces the risk of impact injury by decreasing joint angular velocity, providing damping of impact loads. Muscles protect bone from fracture by resisting bending moments across long bones.”

Currently, the T-Score is most commonly used to determine bone mineral density compared to that of a healthy 30-year-old adult and measured in standard deviations (SD), while the World Health Organization (WHO) defines normal bone mineral density (BMD) as a Tscore > -1, osteopenia as a T-score of -1 to -2.5, osteoporosis as a T-score below -2.5, and severe osteoporosis as a T-score below -2.5 in combination with previous fragility fracture. However, the change in bone density by percentage appears to be more representative of the amount of bone loss observed in the hips and trochanter as noted in the clinical data collected from the ISS long duration astronaut population.

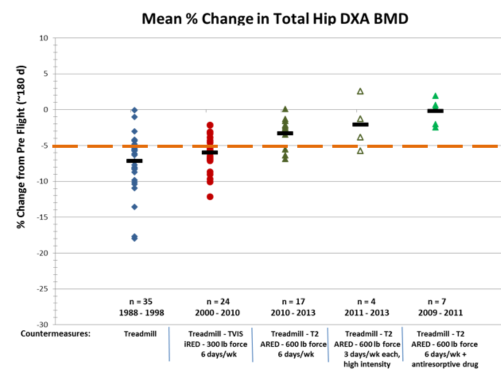
Level	Definition
Normal	Bone density is within 1 SD (+1 or −1) of the young adult mean.
Low bone mass	Bone density is between 1 and 2.5 SD below the young adult mean (−1 to −2.5 SD).
Osteoporosis	Bone density is 2.5 SD or more below the young adult mean (−2.5 SD or lower).
Severe (established) osteoporosis	Bone density is more than 2.5 SD below the young adult mean, and there have been one or more osteoporotic fractures.

World Health Organization Definitions Based on Bone Density Levels

Reference Data

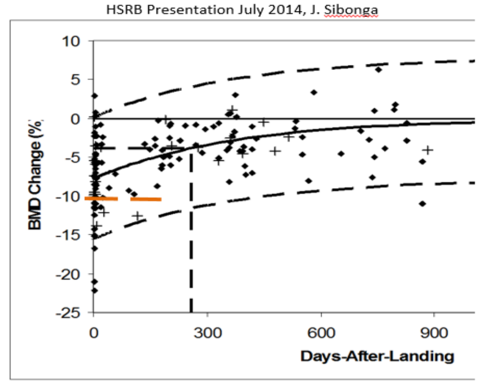
"Observations of astronauts and cosmonauts indicate that the skeletal unloading causes loss of calcium from the skeleton, which increases the risk of kidney stones and bone fracture (during the mission and potentially life long consequence). By using single photon absorptiometry, the bone density of the calcaneus in astronauts aboard Skylabs 2, 3, and 4 had a decrease of as much as 8% with an average of 4% on the longest flights of 59 and 84 days. Similar observations have been made in cosmonauts, where losses in bone density of the calcaneus have been reported to be as much as 19% after 140 days in microgravity." (Holick) Additionally, Shackelford et al., reported "to date, we have collected pre-and post-flight bone densitometry measurements on 47 individuals from such flights. Although losses show significant heterogeneity among individuals and between bones of a given subject, bone loss is a consistent finding after spaceflight. Among astronauts and cosmonauts who participated in long duration (average of 170 days) flights aboard Mir and the ISS, >50% of the crew members had a 10% loss in at least one skeletal site, and 22% of the Mir cosmonauts had a 15–20% loss in at least one site. This bone loss has been shown to be a regional phenomenon in which the areas with the greatest decrease in weight bearing lose the most bone; losses average 1–2%/mo in such regions as the lumbar spine and hip compared with no change in the arms or radius (Mir and ISS astronauts, arms: 0.1%/mo; ISS astronauts, radius and ulna: -0.1%/mo)."

13718 - January 2014 Bone Lab Data Analysis



BMD Recovery Trochanter

HSRB Presentation July 2014, J. Sibonga



In a review of the information from the Apollo Medical Summit, NASA/TM-2007-214755, it was noted that "the astronauts demanded exercise capability for the CM for rest and relaxation purposes," which supports [V1 4108] and [V1 4111] of NASA-STD-3001 stating that countermeasures should be used to "mitigate undesirable physical, physiological, and psychological effects of space flight upon crewmembers."

Due to the rarity of persons in microgravity for the purposes of studying bone loss, numerous studies have been performed using bed-rest as an analogue to better understand the physiology during skeletal unloading, as well as efficacy of various prevention techniques (exercise, medications, diet, etc). The tables show the various results of these studies and the impact of unloading regardless of the presence of microgravity. (Tables 1 and 2 from Grimm et al.)

Reference Information

Table 1
Recent bed-rest studies investigating the influence of simulated microgravity on bone.

Type of bed-rest	Duration	Observations	Reference
HDT with or without exercise	5 d	Bone resorption increased during BR, locomotion replacement training or 25 min of upright standing had no effect	[176]
HDT with or without resistive vibration exercise or resistive exercise	60 d	Increases of sclerostin and dickkopf-1 in all groups, no evidence for an influence of exercise on the rise in serum sclerostin and dickkopf-1 levels	[177]
HDT with or without resistive vibration exercise	60 d	Serum osteocalcin was significantly associated with serum insulin and leptin (increased during BR in both groups)	[178]
HDT	35 d	Increased bone demineralization, increased urinary calcium and decreased aquaporin-2 excretion	[179]
HDT with or without 30 min centrifugation (1 g at center of mass)	5 d	Serum sCD200 levels fall and sCD200R1 levels rise (the author proposes them as useful surrogate markers for bone loss). Centrifugation abolished or attenuated these changes.	[180]
HDT	14 and 21 d	The Wnt-pathway is involved in bone loss under microgravity. Sclerostin levels rose during BR and declined at the ends of the studies. Bone formation marker PINP decreased and bone resorption marker NTx increased during BR	[124]
HDT	30 d	Urinary markers of bone resorption increased, and serum parathyroid hormone decreased. Urinary oxalate excretion decreased and correlated inversely with urinary calcium	[49]
HDT	90 d	Bone mineral density declined significantly, serum sclerostin was elevated. Serum PTH levels were reduced, urinary bone resorption markers and calcium were significantly elevated	[181]
HDT with or without vibration training	14 d	Increase in bone resorption, no effect of vibration on bone resorption markers, bone formation markers, and calcium excretion.	[182]
HDT with or without exercise or high-protein nutrition	60 d	Deterioration of bone microstructure and density, no effect of exercise and nutrition.	[183]
HDT with or without exercise or high-protein nutrition	60 d	Regional differences in bone loss in women with incomplete recovery one-year after bed-rest. No effects of exercise or nutrition	[184]
HDT	21–90 d	No changes in phylloquinone, urinary γ-carboxyglutamic acid, or undercarboxylated osteocalcin, comparable to spaceflights, indicating that vitamin K supplementation in microgravity is not needed to counteract bone loss	[185]
HDT with or without resistive vibration exercise or resistive exercise	60 d	Reductions in cortical area, cortical thickness and bone density at the distal tibia, but increases in periosteal perimeter and trabecular area. Recovery within 180 d after BR. At the distal radius, persistent increases in cortical area, cortical thickness, cortical density and total density and decreases in trabecular area. Resistive vibration exercise had a significant effect only on the cortical area at the distal tibia.	[186]

BR = bed-rest, HDT = head down tilt, d = days, NTx = amino-terminal collagen crosslinks, PINP = procollagen type I N-terminal propeptide, sCD200 = soluble CD200, cCD200R1 = soluble CD200R1.

Table 2
Overview of the bone loss countermeasures used in real and simulated microgravity.

Countermeasure	Microgravity stimulus	Duration	Observations	Reference
iRED	Real (ISS)	6 months	No effects on bone loss	[42]
ARED	Real (ISS)	6 months	Helps maintaining bone mass when combined with adequate energy intake	[42]
70 mg alendronate once/week + iRED or ARED	Real (ISS)	5.5 months	High variability of data, hints towards superiority of combination *vs.* training alone	[107]
HEM (resistance exercise training)	Simulated (horizontal bed-rest)	17 weeks	Prevention of BMD loss in total hip, calcaneus, pelvis and total body, significantly increased bone metabolism markers and net calcium balance	[149]
Resistive exercise ± vibration	Simulated (HDT bed-rest)	60 d	The combination of vibration and resistive exercise prevents bone loss at the tibial diaphysis and proximal femur more efficiently than resistive exercise alone	[150]
Supine treadmill exercise within LBNP/flywheel resistive exercise	Simulated (HDT bed-rest)	60 d	Exercise treatment significantly attenuated loss of hip and leg bone mineral density	[51]
Artificial gravity (1 g at center of mass)	Simulated (HDT bed-rest)	3 × 5 d	No protection by artificial gravity	[100]
Alendronate (10 mg/d)	Simulated (horizontal bed-rest)	17 weeks	Alendronate attenuated most of the changes in bone occurring during bed rest	[158]
EHDP (5 or 2 × 20 mg/d)	Simulated (horizontal bed-rest)	20 weeks	Only minor effects, no change in skeletal mineral loss	[161]
Flywheel resistance training + 1 × 60 mg pamidronate 14 d before start of bed-rest	Simulated (HDT bed-rest)	90 d	No effect of pamidronate on bone metabolism	[160]

HEM = horizontal exercise machine, BMD = bone mineral density, iRED = interim resistive device, ARED = advanced resistive exercise device, HDT = head down tilt, d = days, LBNP = lower body negative pressure, EHDP = disodium ethane-1-hydroxy-1,1-diphosphonate or ethane-1-hydroxy-1,1-diphosphonate.

Grimm et al.

Vol 1: 4.2.9; Appendices F6, F8
Vol 2: 7006, 7038-7039

Application

Information noted in the NASA-STD-3001 Volumes 1 and 2, along with details from the HIDH provide the reference details and guidance to aid in the understanding of the needs of the crew. Some examples that have helped in the implementation of the exercise equipment include items from ISS, like:

- Advanced Resistive Exercise Device (aRED) – This device, while similar to the iRED, was capable of higher concentric resistance and eccentric-to-concentric ratio close to that recommended by expert panels and confirmed effective by exercise scientists . The ARED also collects data regarding the parameters associated with crew exercise, and transmits it to the ground.
- Treadmill 2 (COLBERT) – An exercise treadmill that can also be used to collect data such as body loading, duration of session, and speed for each crewmember.
- Cycle-Ergometer with Vibration Isolation System (CEVIS) – A structurally isolated aerobic exercise cycle that serves as a countermeasure to cardiovascular deconditioning on orbit.

NASA astronaut Chris Cassidy gets a workout on the advanced Resistive Exercise Device (aRED) in Node 3.

ESA astronaut Luca Parmitano exercises on the Combined Operational Load Bearing External Resistance Treadmill (COLBERT).

The crew members are required to exercise a minimum of time dependent on the program mission as dictated by the medical team, however previous requirements have been as little as 2.5 hours per workday with a strict exercise program. Additionally, the medical team may instruct the crew to take medication, like bisphosphonates, to prevent bone loss, but this is not currently required for all crew.

Furthermore, the food lab and nutritionists have developed appropriate nutritionally foods to ensure that the crew have enough micro- and macronutrients to promote crew mental and physical health. The interactions of the various standards from both Volume 1 and 2, along with the supported information from the appendices will allow for successful missions.

While the individual standards that address the crew health or a related areas, considerations should be taken to ensure that all the standards are reviewed holistically so they can be applied appropriately for planning and future requirements.

ESA astronaut Samantha Cristoforetti exercises on the Cycle Ergometer with Vibration Isolation and Stabilization (CEVIS) in the Destiny Laboratory.

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